IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
YASUHIDE TACHI ET AL	)	Examiner: Roberts
Serial No. 024,111	)	Art Unit: 125
Filed: March 26, 1979	)	
For: NOVEL HYDROCORTISONE DERIVATIVE	)	

RESPONSE TO FINAL REJECTION (Paper No. 11)

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

The undersigned attorney wishes to thank the Examiner for his time and courtesy in the interview of March 10, 1980. While the interview was not successful in reaching agreement as to allowable subject matter, agreement was reached as to a proper definition of the issue of patentability presented here. The interview also provided insights as to what the Examiner considers weaknesses in applicants' case and thereby afforded the applicants the opportunity to supplement the record with the Declaration of Mr. Yasuhide Tachi, submitted herewith. The Examiner and the undersigned agreed that due to mutual oversights the issue of patentability had not previously been properly defined.

At the outset of the interview the undersigned informed the Examiner that he had unintentionally misrepresented the teachings of the primary reference, the patent to Ercoli et al. In the previous response the undersigned attorney directed the Examiner's attention to the teaching of Ercoli et al at column 4, lines 13-52 which is probably the most relevant prior art teaching.

However, the undersigned misrepresented that teaching where he stated that Ercoli et al do not disclose any diester of hydrocortisone. In fact, at column 4, line 49 Ercoli et al disclose "cortisol 17 alpha-valerate-21-acetate." The error was occasioned by the difference in nomenclature and was unintentional. The undersigned, prior to the interview, came to the realization that "cortisol" is a synonym for "hydrocortisone."

At the interview the undersigned acknowledged that the aforementioned teaching of Ercoli et al probably establishes prima facie obviousness. The discussion at the interview then focused on applicants' evidence that the claimed compound possesses unexpected properties, which evidence tends to rebut the prima facie case of obviousness and to establish patentability. The argument that evidence of record establishes unexpected properties and serves to prove patentability was previously advanced at page 4 of applicants' response filed November 2, 1979 which directed attention to the comparative tests reported at pages 4 and 5 of the present specification. In those tests reported in applicants' specification the claimed compound (I) was compared with closest known prior art compound, i.e. hydrocortisone 17-valerate-21-acetate fo Ercoli et al. In the tests for vasoconstriction reported there, claimed compound (I) showed an average score of 2.47 whereas the closest prior art diester showed an average score of 1.93. The request for an interview was prompted by the fact that in the office action of March 10, 1980 the Examiner did not address applicants' argument that these tests reported in their specification establish unexpected superiority and are compelling evidence of patenability.

It now appears that the undersigned has erred in greatly understating applicants' case of patentability based on the aforementioned comparative test data. Both the undersigned and the Examiner viewed the difference in average score in the vasoconstriction test between the claimed compound and the closest prior art compound, i.e. the difference between 2.47 and 1.93, as amounting to a 28 percent increased therapeutic effectiveness. The new test data submitted herewith in the Declaration by Mr. Tachi establishes that applicants' claimed compound is in reality 10 times as effective as the closest prior art diester. The data presented in Mr. Tachi's declaration demonstrates that the claimed compound when present in a concentration of 0.01 percent in the same petrolatum-based ointment mentioned at page 4 of the specification, produces an "average score" equal to that produced by that produced by the prior art compound at a concentration 10 times as great, i.e. 0.1 percent (see page 4, line 15). In other words, applicants' claimed compound possesses 10 times the therapeutic effectiveness of the closest prior art compound.

The other points touched upon in the interview will now be mentioned, not necessarily in their order of importance.

At the interview it was noted that Ercoli et al, at column 4, lines 50-52 teach that mixed diesters produced by "acylating at the 21-position in the presence of a preformed 17 alpha-acyloxy group" increase the solubility of the hormone in the therapeutic carrier as compared to the 17 monoester. Ercoli et al do not teach that the introduction of a second ester group at the 21-position increases therapeutic effectiveness. An increased concentration in the carrier of the same compound might well increase the therapeutic effectiveness of that particular compound. However, where one changes the compound by introduction of a second ester group at the 21-position the result may be an increase in solubility but this does not

necessarily lead to increased therapeutic effectiveness. The truth of the foregoing is established by the data of applicants' Table 1 (Page 5 of the specification). For example, the data of Table 1 shows that modification of hydrocortisone 17-butyrate by introduction of a second ester group at the 21 position to form hydrocortisone 17, 21 dibutyrate resulted in the lowering of the therapeutic effectiveness as indicated by a decrease in the average score from 1.70 to 1.57. Regardless, the point is considered moot because the issue here is not the patentability of applicants' diester over a prior art monoester. Rather, here the issue is the patentability of applicants' claimed diester over a homologous prior art diester. There is absolutely nothing in the teachings of Ercoli et al which would lead one to expect that applicants' claimed compound (I) would be 10 times as effective as the closest prior art compound, i.e. "cortisol 17 alpha-valerate-21-acetate" (Ercoli et al column 4, line 49).

At the interview the Examiner admitted that he erred in citing Elks et al '591 instead of '590 which applicants' brought to his attention. The Examiner further conceded that neither of the secondary references suggests that any improvement will result from converting a monoester to a diester. In other words, they do not contain a teaching in support of the proposition for which they were cited. However, the Examiner maintains that an improvement in therapeutic effectiveness achieved by converting the monoester to a diester is well known in the prior art and he cited Elks et al '590 and British 1,202,001 in support of his position.

The British reference, at page 1, lines 36-40 teaches that the introduction of a second ester group at the 17 position of a 21-monoester produces "a significant increases in topical activity as evidenced by bioassays especially designed for measuring the anti-flammatory activity of a given substance by topical application (e.g. the vasoconstriction test)." However, note that the primary reference, the patent to Ercoli et al, discloses monoesters with the ester group in the 17-position. Therefore, one could not improve the therapeutic effectiveness of the compounds of Ercoli et al by introducing a second ester group at the 17-position as arguably suggested by the British reference because the 17-position of the compounds of Ercoli et al is already occupied. Applicants can find nothing in the teachings of Elks et al '590 that would suggest that any improvement would be provided by esterfication of the 21-position. However, again the point is considered moot. The issue is not the patentability of applicants' diesters over a prior art monoester but, rather, the patentability of applicants' diester over the cloest prior art diester.

At the interview, the Examiner suggested that the test data of applicants' specification should not be given weight because it was not submitted in a form of a separate declaration. Applicants respectfully submit that the Examiner is wrong as a matter of law. The original specification is itself submitted as a Declaration and no further Declaration is required. See for example Ex parte Drewe 203 USPQ 1127(P.O.Bd.App. 1977) and In re Kollman, 201 USPQ 193 (CCPA 1979).

In conclusion it is respectfully requested that the Examiner reconsider the rejection of record from the point of view that Applicants' claimed compound possesses 10 times the

therapeutic effectiveness of that possessed by the closest prior art compound. Admittedly, the degree of superiority necessary to rebut a prima facie case of obviousness is a somewhat subjective determination and will vary from case to case, but it is submitted that a 10-fold increase is clearly sufficient in this regard. Those skilled in the art would have no reason to expect, from a reading of the references, that the claimed diester would have any degree of superiority over a homogolous diester.

It is submitted that a fair reappraisal of the rejection in light of the factual information newly provided by the Declaration of Mr. Tachi will compel a conclusion that the sole claim of record is patentable over the prior art.

Respectfully submitted,

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Dated: June 9, 1980

Enclosure: Declaration